The existence of Adrenal Insufficiency in Patients with COVID-19 Pneumonia

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Article

Keywords: Adrenal insufficiency, long covid syndrome, COVID-19 pneumonia

Posted Date: July 28th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3157398/v1

Abstract

Introduction: Infection with SARS-CoV-2 virus may result in long COVID, a syndrome characterized by symptoms such as dyspnea, cardiac abnormalities, cognitive impairment, and fatigue. One potential explanation for these symptoms is adrenal insufficiency (AI).

Objective: To evaluate the prevalence of AI in patients with a history of COVID-19 pneumonia.

Methods: Cross-sectional study of patients who were aged ≥ 18 years and had a 3-month history of radiography-confirmed COVID-19 pneumonia. Exclusion criteria included current or previous treatment with glucocorticoids and use of an oral contraceptive. Adrenal function was evaluated using a low dose (1ug) corticotropin stimulation test (CST). Serum cortisol levels were measured at 0, 30, and 60 minutes, and baseline plasma ACTH was also measured.

Results: Of the 41 patients enrolled, the median age was 62 years, 17 (42%) were female, and all 41 (100%) had severe pneumonia at baseline. Eleven patients (27%) had AI, as evidenced by hypocortisolism (mean serum cortisol 198.92 nmol/L, standard deviation 83.87, range 84.15–289.42). Of these 11 patients, 10 (91%) had secondary AI (median ACTH 6.27 pmol/L, range 4.98–9.95 pmol/L) and one had primary AI (mean ACTH 32.78 pmol/L). Six of the 11 patients with AI (54.5%) reported symptoms of persistent fatigue and 5 (45.5%) required regular glucocorticoid replacement.

Conclusions: Our results suggest that AI, predominantly caused by pituitary disruption, may emerge after SARS-CoV-2 infection and should be considered in patients with a history of COVID-19 pneumonia with or without clinical hypocortisolism.

Introduction

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 31, 2019. Since then, the disease has persisted as a global pandemic due to the emergence of multiple SARS-CoV-2 variants. To date, more than 600 million confirmed cases of COVID-19 have been reported worldwide (1). Many people with COVID-19 suffer from long-lasting symptoms, collectively known as long COVID, which is characterized by the persistence of fatigue, headache, dyspnea, and brain fog more than 12 weeks after the onset of illness (2, 3). SARS-CoV-2 infects human cells *via* interactions between the viral Spike glycoprotein and host angiotensin-converting enzyme 2 (ACE2) receptor (4). Infection of brain tissue has been suggested to be one possible mechanism underlying the neurological symptoms experienced by some COVID-19 patients.

In a previous study, Leow et al. (5) evaluated function of the hypothalamic–pituitary axis in 61 COVID-19 patients and reported evidence of hypocortisolism in 40% of the cohort. The mechanisms proposed were reversible hypophysitis or direct hypothalamic damage caused by the virus (5). However, there is currently limited data available on the prevalence and causes of adrenal insufficiency (AI) following SARS-CoV-2 infection. The aim of this study was to evaluate the prevalence of AI in adult patients who had a 3-month history of COVID-19 pneumonia.

Materials and Methods

Study design

This was a cross-sectional study that enrolled consecutive patients with a history of COVID-19 pneumonia of 3 months duration at Chulabhorn Hospital, Chulabhorn Royal Academy, Thailand. The study was approved by the Human Research Ethics Committee Chulabhorn Research (Project code 140/2564) and was conducted in accordance with the Declaration of Helsinki and its amendments. All participants provided written informed consent prior to inclusion. The study was registered at the Thai Clinical Trials Registry (TCTR20220606002).

Participants

Participants were recruited from a COVID-19 cohort ward and acute respiratory unit clinic at Chulabhorn Hospital between March 1, 2022 and April 20, 2022. Eligible patients had a 3-month history of COVID-19 pneumonia and were aged ≥ 18 years. A diagnosis of COVID-19 was confirmed by real-time reverse-transcriptase polymerase chain reaction of SARS-CoV-2 RNA in nasopharyngeal swab specimens. The severity of COVID-19 was defined as critical, severe, and non-severe according to the World Health Organization (WHO) criteria (6). Critical COVID-19 was defined by as acute respiratory distress syndrome, sepsis shock, sepsis, or the need for life-sustaining therapies such as mechanical ventilation or vasopressor therapy. Severe COVID-19 was defined as one or more of (a) oxygen saturation < 90% on room air, (b) signs of pneumonia, or (c) signs of severe respiratory distress. Non-severe COVID-19 was defined as the absence of any criteria for severe or critical COVID-19. Pneumonia was confirmed by imaging with either a chest radiograph or computed tomography (CT) of the chest. Among the exclusion criteria were comorbidity with pituitary disease or adrenal disease; unstable clinical condition; chronic kidney disease (creatinine > 1.5 mg/dL); severe hepatitis (alanine aminotransferase > 1.5× upper limit of normal); pregnancy or plans to become pregnant; and concurrent use of oral contraceptive pills, steroids (oral, inhaled, topical, or intra-articular), and other medications known to affect cortisol-binding globulin (including oral estrogens). Suitable subjects identified from a review of case notes were contacted in person or *via* the telephone.

Image analysis

COVID-19 pneumonia was confirmed by radiography or CT scan. CT scans were performed on the first and second day after COVID-19 diagnosis. The severity of pneumonia on CT was scored according to the COVID-19 Reporting And Data System (CO-RADS) classification using lobar-based assessment. In brief, each of the five lung lobes was subjectively scored from 0 to 5 (0, no involvement; 1, < 5% involvement; 2, 6–25% involvement; 3, 26–50% involvement; 4, 51–75% involvement; 5, ≥ 76% involvement). The total score was the sum of the individual lobar scores and ranged from a minimum of 0 to a maximum of 25. Total scores of < 7, 8–17, and 18–25 were classified as mild, moderate, and severe pneumonia, respectively (7).

Study protocol

Blood samples were collected at baseline for measurement of plasma ACTH and serum cortisol, free thyroxine (FT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin (anti-Tg), and anti-thyroid peroxidase (anti-TPO). Corticotropin stimulation tests (CSTs) were performed as described below. Participants with AI were evaluated for potential causes other than SARS-CoV-2 infection by magnetic resonance imaging (MRI) of the pituitary gland or an adrenal CT protocol as appropriate.

Corticotropin stimulation tests

Low-dose (1 μg) CSTs were performed between 8 am and 10 am. An intravenous catheter was inserted into an antecubital vein and 0.4 mL (1 μg) of a synthetic ACTH 1–24 solution (Synacthen®, Novartis, Chippenham, UK) in 0.9% sodium chloride was administered through the catheter, followed by flushing with 15 mL of 0.9% sodium chloride. Blood samples were collected immediately before Synacthen injection to determine baseline ACTH and cortisol, and at 30 min and 60 min after Synacthen injection to determine the cortisol response to stimulation. A diagnosis of AI was defined as a peak cortisol level of < 402.81 nmol/L based on the new criteria for the Roche Elecsys Cortisol II Assay (8, 9). Primary AI was defined as a baseline plasma ACTH level > 2× the upper limit of the reference range (10).

Laboratory investigations

Serum cortisol and plasma ACTH were measured using automated electrochemiluminescence immunoassays (Roche Elecsys Cortisol Generation II assay and Roche Elecsys ACTH assay; Roche Diagnostic, Mannheim, Germany). For plasma ACTH measurement, blood was collected in EDTA tubes and immediately transferred to the laboratory. FT4, TSH, anti-Tg,

and anti-TPO were also measured using automated electrochemiluminescence immunoassays on the Roche Elecsys system. Reference ranges were 2.86–13.86 pmol/L for plasma ACTH, 11.97–21.88 pmol/L for FT4, and 0.27–4.2 mIU/L for TSH.

Statistical analysis

The sample size calculation was based on an infinite population proportion formula (11) and previous analysis of the prevalence of AI in SARS-CoV-2 patients (5). Data analysis was conducted using STATA/SE version 16.1 (StataCorp LP, College Station, TX, USA). Continuous data are presented as mean ± standard deviation (SD) or the median with interquartile range (IQR) as appropriate. Normally distributed continuous data were compared using a Student's t-test for two groups or by one-way analysis of variance for three or more groups. Non-normally distributed continuous data were compared using the Mann–Whitney U test for two groups or the Kruskal–Wallis test with Dunn's post hoc test for three or more groups. Categorical data were compared using a Chi-squared test. The relationship between two continuous variables was determined using Pearson's correlation. The α level for statistical significance was set at 0.05.

Results

Participants

Medical records of 2719 patients seen at our hospital between March 1, 2022 and April 20, 2022 were reviewed. A total of 2463 patients were excluded (182 patients < 18 years of age, 2 patients were deceased, and 2279 patients had no documentation of pneumonia by radiography). The remaining 256 participants were contacted in person or by telephone and 215 declined to participate. Finally, a total of 41 patients were enrolled in the study (Fig. 1).

The 41 included patients had a median age of 62 years (IQR, 49.5–66.0) and 17 (41%) were female. All of the patients had severe COVID-19 pneumonia at baseline based on the WHO criteria (6). Thirty-seven patients underwent chest CT; based on the CO-RADS system of pneumonia classification (7), 36 of the 37 patients (87.8%) had mild disease and 1 patient (2.4%) had moderate disease. None of the patients developed acute respiratory failure. Most patients were obese (29/41; 70.7%) and the mean body mass index (BMI) of the full cohort was 28.85 kg/m^2. Fifteen patients (36.7%) received dexamethasone treatment for COVID-19. The cumulative dose of dexamethasone in most patients was 15 mg per course whereas one patient received the cumulative dose of 45 mg per course. Other baseline characteristics of the study participants are shown in Table 1.

Table 1
Baseline characteristics of the 41 study participants.

Baseline characteristics	Number (%) or median (IQR)
Sex (female)	17 (41.5%)
Age (years, range)	62 (49.5–66)
BMI (kg/m^2)	28.85 (2(5.52)
Obesity	29 (70.7%)
Diabetes mellitus	13 (31.7%)
Hypertension	23 (56.1%)
Cardiovascular disease	1 (2.4%)
COVID-19 severity (WHO category)	
Critical	0
Severe	41 (100%)
Non-severe	0
Symptoms	
Fever	14 (34.1%)
Upper respiratory tract involvement	34 (82.9%)
Diarrhea	7 (17.1%)
Dyspnea	3 (7.3%)
Fatigue	8 (19.5%)
Rash	2 (4.9%)
Treatment	
Dexamethasone	15 (36.6%)
Favipiravir	38 (92.7%)
Sotrovimab	3 (7.3%)
Convalescent plasma	6 (14.6%)
Abbreviations:	
BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range; WHO, World Health Organization.	

Eleven (27%) of the 41 participants showed evidence of hypocortisolism in the CST (Fig. 2). The mean baseline cortisol level was 198.92 ± 83.87 nmol/L, and 3 patients had baseline cortisol levels < 137.95 nmol/L. Of the 11 patients with hypocortisolism, 10 (90.9%) were diagnosed with central hypocortisolism based on low-to-normal ACTH levels (median ACTH 6.27 pmol/L, IQR 4.98–9.95). The remaining patient had a plasma ACTH level of 32.78 pmol/L and was diagnosed with primary AI. Six of the 11 patients (54.50%) reported persistent fatigue after resolution of the acute infection. Only 5 of the 11 patients received corticosteroid therapy for the treatment of COVID-19 (Table 2). Six of the 10 patients with secondary AI underwent MRI of the pituitary and no abnormal lesions were found. The patient with primary AI underwent an adrenal CT protocol and had normal bilateral adrenal glands.

Table 2
Clinical characteristics and laboratory values of patients with hypocortisolism (n = 11).

Patient ID	Age (years)	Sex	CT score[a]	Treatment	Cumulative dose of Dex (mg)	Persistent fatigue	Cortisol level in CST (nmol/L)			ACTH (pmol/L)
							Baseline	30 min	60 min	
No. 1	73	M	2	Fa, C	None	Yes	199.5	383.5	256.6	12.80
No. 2	29	M	2	Fa, C	None	No	210.8	295.8	218.8	19.07
No. 3	33	M	NA	Fa	None	Yes	106.5	196.7	328.6	6.25
No. 4	63	M	4	S	None	No	284.5	389.8	268.2	32.78
No. 5	51	M	NA	Fa	None	No	230.9	334.9	300.7	6.29
No. 6	46	F	1	Fa, Dex	15	Yes	351.8	381.6	295.2	6.05
No. 7	67	F	2	Fa, Dex	15	Yes	280.6	283.1	390.7	3.70
No. 8	21	M	2	Fa, C	None	Yes	84.1	402.0	250.2	5.41
No. 9	34	F	NA	Fa, Dex	15	No	165.3	379.9	285.3	9.00
No. 10	67	F	1	Fa, Dex	15	No	160.6	350.1	242.2	6.64
No. 11	71	F	6	Fa, Dex	15	Yes	112.8	338.3	346.8	2.82

Abbreviations: ACTH, adrenocorticotropic hormone; C, convalescent plasma; CST, corticotropin stimulation test; CT, computer tomography; Dex, dexamethasone; F, female; Fa, favipiravir; ID, identification number; mg, milligrams; M, male; NA, not available; No, number; S, sotrovimab.

[a] CO-RADS classification.

Two of the 41 patients (5%) had abnormal thyroid function tests; one had primary hyperthyroidism, and positive autoimmune thyroid antibodies. She was being treated with levothyroxine suppressive therapy for papillary thyroid cancer, and the second had subclinical hypothyroidism (thyroid-stimulating hormone 5.4 μIU/mL). Five patients (12%) were positive for anti-thyroid peroxidase or anti-thyroglobulin antibodies with normal thyroid function test. Further clinicopathological details of the study participants is provided in Supplementary Table 1

We performed logistic regression analysis to determine the risk factors associated with AI in the subsets of patients with (n = 11) or without (n = 30) hypocortisolism. Increased BMI (adjusted P = 0.019) was the only significant risk factor for AI. Age, sex, treatment modality, glucocorticoid usage, history of COVID-19 vaccination, and disease severity were not associated with AI (Table 3).

Table 3
Evaluation of risk factors for hypocortisolism by logistic regression.

Characteristic	Patients with hypocortisolism (n = 11)	Patients without hypocortisolism (n = 30)	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex, female	5 (45.5%)	12 (40.0%)	1.25 (0.31–5.04)	0.754		
Age, years (IQR)	51 (33–67)	62 (59–65)	0.95 (0.91–1.00)	0.067	1.04 (0.96–1.12)	0.380
BMI, kg/m^2 (IQR)	34.96 (29.86–37.52)	26.3 (24.61–30.0)	1.23 (1.05–1.43)	**0.009**	1.27 (1.04–1.54)	**0.019**
Comorbidities						
Obesity	10 (90.9%)	19 (63.3%)	5.79 (0.65 – 51.50)	0.115		
Diabetes mellitus	5 (45.5%)	8 (26.7%)	2.29 (0.54–9.64)	0.258		
Hypertension	3 (27.3%)	20 (67.7%)	0.19 (0.04–0.86)	**0.032**	0.17 (0.02–1.23)	0.079
CT score (CO-RADS)						
< 7	7 (72.7%)	28 (96.6%)	4.00 (0.22–72.18)	0.348		
8–17	1 (12.5%)	1 (3.4%)				
≥ 18	0	0				
Laboratory investigations						
SARS-CoV-2 antibody (mean ± SD BAU/mL) [a]	5475.57 ± 4646.10	17425.10 ± 7900.03	0.99 (0.99–1.00)	0.257		
Serum CRP (mg/L)	6.09 (3.33–12.83)	9.68 (4.60–12.76)	1.02 (0.98–1.05)	0.426		
Persistent fatigue	6 (60.0%)	8 (32.0%)	3.19 (0.70–14.56)	0.135		
Treatment						

Abbreviations: BAU, binding antibody unit; BMI; body mass index, CI, confidence intervals; CRP; C-reactive protein; CO-RADS, COVID-19 Reporting And Data System; CT, computed tomography; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

[a] Based on the WHO international standard for anti-SARS-CoV-2 Ig. One Elecsys-S unit = 0.972 × binding antibody unit.

[b] 10 of the 11 patients with hypocortisolism had documentation of COVID-19 vaccination

Characteristic	Patients with hypocortisolism (n = 11)	Patients without hypocortisolism (n = 30)	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Dexamethasone	5 (45.5%)	10 (33.3%)	1.67 (0.41–6.82)	0.477		
Favipiravir	10 (90.9%)	28 (93.3%)	0.71 (0.06–8.76)	0.792		
Sotrovimab	1 (9.1%)	2 (6.7%)	1.40 (0.11–17.17)	0.792		
Convalescent plasma	3 (27.3%)	3 (10.0%)	3.38 (0.57–20.10)	0.181		
COVID−19 vaccine[b]						
CoronaVac	2 (20.0%)	7 (23.3)	0.82 (0.14–4.80)	0.827		
BBIBP-CorV	2 (20.0%)	4 (13.3%)	1.63 (0.25–10.58)	0.611		
ChAdOx1-S	8 (80.0%)	24 (80.0%)	1.00 (0.17–5.98)	1.000		
BNT162b2	5 (50.0%)	22 (73.3%)	0.36 (0.08–1.60)	0.180		
mRNA-1273	2 (20.0%)	2 (6.7%)	3.50 (0.42–28.91	0.245		

Abbreviations: BAU, binding antibody unit; BMI; body mass index, CI, confidence intervals; CRP; C-reactive protein; CO-RADS, COVID-19 Reporting And Data System; CT, computed tomography; IQR, interquartile range; OR, odds ratio; SD, standard deviation.

[a] Based on the WHO international standard for anti-SARS-CoV-2 Ig. One Elecsys-S unit = 0.972 × binding antibody unit.

[b] 10 of the 11 patients with hypocortisolism had documentation of COVID-19 vaccination

Discussion

The results of our study suggest that AI is a common complication in patients with COVID-19 pneumonia, with most cases in our cohort (10 of 11 patients) manifesting as central hypocortisolism. Additionally, a significant proportion of patients in our study (55%) reported clinical symptoms of long COVID, including fatigue, insomnia, and dyspnea.

The underlying mechanism of AI in COVID-19 patients is likely to involve the ACE2 receptor, the major functional receptor for infection by both SARS-CoV and SARS-CoV-2. Indeed, ACE2 mRNA has been detected in many human tissues, including endocrine glands such as the adrenal and pituitary glands (12–15). ACE2 receptors mediate viral entry in concert with S glycoprotein priming by the host cell transmembrane serine protease 2 (12, 13).

Many studies have reported cases of pituitary disruption after SARS-CoV-2 infection, including central AI, central diabetes insipidus, hypothalamic hypogonadism, lymphocytic hypophysitis, and pituitary apoplexy. Primary AI has also been reported in COVID-19 patients. Details of previously reported cases of pituitary dysfunction and primary AI occurring more than 2 weeks after SARS-CoV-2 infection are shown in Table 4 (16–25). The findings from those studies are consistent with our own results and support the conclusion that pituitary and adrenal function may be affected by SARS-CoV-2 infection.

Table 4

Literature cases of hypothalamic–pituitary dysfunction and primary adrenal insufficiency occurring more than 2 weeks after SARS-CoV-2 infection.

Study (ref. no.)	Patient age/sex	Time to onset after infection	Presentation	Results of investigations	Diagnosis
Secondary adrenal insufficiency					
Kenya et al. (17)	23/F	1 month	Fatigue, nausea, vomiting	• Basal cortisol 226.24 nmol/L; ACTH 1.08 pmol/L • AI was confirmed with insulin tolerance test. • MRI pituitary: normal.	Secondary adrenal insufficiency
Central diabetes insipidus					
Sheikh et al. (21)	28/M	1 month	Polyuria, polydipsia, increased thirst	• 24-hr urine volume 7 L. • Serum sodium 153 mmol/L; paired serum and urine osmolality 300 and 93 mOsm/kg, respectively; urine sodium 16 mOsm/kg. • MRI brain: normal.	DI with concomitant myocarditis
Yavari et al. (20)	54/F	6 weeks	Thirst, polyuria, polydipsia	• 24-hr urine volume 13.3 L. • Serum sodium 144 mmol/L; paired serum and urine osmolality 298 and 164 mOsm/kg, respectively. • Urine osmolality 810 mOm/kg after intravenous desmopressin administration test. • MRI pituitary: normal.	CDI
Misgar et al. (16)	60/F	8 weeks	Polyuria	• 24-hr urinary volume 6 L. • Serum sodium 152 mmol/L; paired serum and urine osmolality 300 and 177 mOsm/kg, respectively. • MRI pituitary: enlarged pituitary with absent posterior pituitary bright spot on T1-weighted images; thickening of pituitary stalk.	CDI
Pituitary apoplexy					

Abbreviations: ACTH, adrenocorticotropic hormone; CDI, central diabetes insipidus; CT, computer tomography; DI, diabetes insipidus; F, female; FSH, follicle-stimulating hormone; FT4, Free thyroxine; GnRH, gonadotropin-releasing hormone; hr, hour(s); LH, luteinizing hormone; M, male; MRI, magnetic resonance imaging; min, minutes; no., number; PAI, primary adrenal insufficiency; TRH, thyrotropin-stimulating hormone; ref, reference; TSH, thyroid-stimulating hormone.

[a] Only the abstract was available in English

Study (ref. no.)	Patient age/sex	Time to onset after infection	Presentation	Results of investigations	Diagnosis
Secondary adrenal insufficiency					
Liew et al. (19)	75/M	1 month	Sudden onset severe frontal headache	• FT4 6.9 pmol/L (reference range: 10.5–24.5), TSH 0.1 mU/L (0.27–4.2), cortisol 57 nmol/L (133–537), testosterone < 0.5 nmol/L (6.7–25.7), LH < 1.0 U/L (1.7–8.6). • MRI: pituitary macroadenoma with recent hemorrhage.	Pituitary apoplexy with hypopituitarism
Hypothalamic hypogonadism					
Soejima et al. (22)	36/M	99 days	Insomnia, headache, dysgeusia, alopecia	• Free testosterone 19.09 pmol/L (22.56–61.42), FSH 4.2 IU/L (1.3–17), LH 3.0 IU/L (0.52–7.8). • MRI pituitary: partially empty sella.	Hypothalamic hypogonadism
Facondo et al. (18)	36/F	6 months	Secondary amenorrhea	• Estradiol < 91.77 pmol/L (91.77–921.42), FSH 3.85 IU/L (3.0–8.0), LH 0.29 IU/L (1.8–11.78), TSH 1.71 mIU/L (0.27–4.2). • GnRH analog test: normal response. • TRH test: delayed response • MRI brain and pituitary: uncertain pituitary microadenoma 3 mm.	Hypothalamic amenorrhea
Lymphocytic hypophysitis					

Abbreviations: ACTH, adrenocorticotropic hormone; CDI, central diabetes insipidus; CT, computer tomography; DI, diabetes insipidus; F, female; FSH, follicle-stimulating hormone; FT4, Free thyroxine; GnRH, gonadotropin-releasing hormone; hr, hour(s); LH, luteinizing hormone; M, male; MRI, magnetic resonance imaging; min, minutes; no., number; PAI, primary adrenal insufficiency; TRH, thyrotropin-stimulating hormone; ref, reference; TSH, thyroid-stimulating hormone.

[a] Only the abstract was available in English

Study (ref. no.)	Patient age/sex	Time to onset after infection	Presentation	Results of investigations	Diagnosis
Secondary adrenal insufficiency					
Joshi et al. (23)	18/F	3 weeks	Acute onset headache	• Hormonal workup: within normal limits. • MRI brain: diffuse thickening and enlargement of the infundibulum with homogenous contrast enhancement.	Lymphocytic hypophysitis
Gorbova et al. (30)[a]	35/F	2 months	Symptoms of hypopituitarism	• Hormonal workup: hypothyroidism, hypocorticism, hypogonadism. • MRI: hypophysitis.	Hypophysitis and reversible hypopituitarism
Primary adrenal insufficiency					
Eskandari et al. (24)	18/M	2 weeks	Severe weakness, acute chest pain, hypotension	• Serum sodium 129 mmol/L; 8 am cortisol 38.63 nmol/L; ACTH > 396 pmol/L. • Cortisol levels at baseline and 60 min after 250 µg ACTH stimulation test were 49.67 and 281.42 nmol/L, respectively. • Anti-21-hydroxylase antibody: positive.	Autoimmune PAI and myocarditis
Machado et al. (31)	46/F	3 weeks	Malaise, nausea, vomiting, hyperpigmentation, postural hypotension	• CT abdomen: adrenal infarction.	PAI with bilateral adrenal infarction
Sánchez et al. (25)	65/F	5 months	Abdominal pain nausea, vomiting, weight loss	• Serum sodium 117 mmol/L • Cortisol at baseline 71.73 nmol/L; ACTH at baseline 427.68 pmol/L • Cortisol at baseline, 30, and 60 min in 250 µg ACTH stimulation test were 63.46, 80.01, and 71.73 nmol/L, respectively • Anti-21-hydroxylase antibody: present. • CT abdomen: unremarkable.	Autoimmune PAI

Abbreviations: ACTH, adrenocorticotropic hormone; CDI, central diabetes insipidus; CT, computer tomography; DI, diabetes insipidus; F, female; FSH, follicle-stimulating hormone; FT4, Free thyroxine; GnRH, gonadotropin-releasing hormone; hr, hour(s); LH, luteinizing hormone; M, male; MRI, magnetic resonance imaging; min, minutes; no., number; PAI, primary adrenal insufficiency; TRH, thyrotropin-stimulating hormone; ref, reference; TSH, thyroid-stimulating hormone.

[a] Only the abstract was available in English

In the present study, high BMI patients was significantly associated with an increased risk of AI. This could be explained by high ACE2 expression in adipose tissue resulting in an increased viral burden, thereby increasing virus-associated damage to the endocrine glands (15). Other potential mechanisms are an increased proinflammatory phenotype

associated with metabolic dysfunction and dysregulation of the renin–angiotensin pathway (26). Obesity is also an important risk factor for increased severity of COVID-19.

Our study results differ from those of Clarke et al. (27) who previously found no evidence of AI in patients with COVID-19 (27). However, the two studies differed in that we performed the CST using a low dose (1 μg) of ACTH whereas Clarke et al. used the standard CST (250 μg ACTH), which may have failed to detect patients with mild or early onset AI (28). The results of our study are similar to those of Urhan et al. (29) except that the frequency of patients with hypocortisolism was higher in our study (27% *vs* 16.2%). This may be due to differences between the two studies in the severity and duration of COVID-19, especially because all of our study participants had severe COVID-19 pneumonia. Another difference between the two studies was that we evaluated adrenal function within 3 months of SARS-CoV-2 infection compared with the study of patients at 3–7 months post-infection by Urhan et al. (29).

A strength of our study is that we used a high cut-off value for serum cortisol (402.8 nmol/L) to define AI, which likely decreased the false-positive rate (8, 27). We also evaluated adrenal function with a low-dose CST to decrease false-positive results. Finally, we performed imaging studies to investigate other potential causes of AI in most of the 11 study participants with AI. Conversely, there are some limitations to our study. The sample size was small and the study was conducted at a single center, both of which may limit the generalizability of the results. In addition, all of the study participants had severe COVID-19 pneumonia, and the results may not be representative of patients with milder forms of the disease.

Overall, the results of this study highlight the importance of monitoring for endocrine complications in patients with a history of SARS-CoV-2 infection. Further research will be needed to fully understand the underlying mechanisms of AI following SARS-CoV-2 infection, and additional studies with larger sample sizes are needed to confirm the findings of this study and to better understand the prevalence and mechanisms of AI in patients with COVID-19 pneumonia.

We conclude that patients with a history of COVID-19 pneumonia who present with clinical symptoms such as shock, nausea, vomiting, and fatigue should have AI excluded as a potential diagnosis. These patients should also be followed longer-term to understand the persistence of AI and its recovery rate. Finally, all patients who suffer from long COVID syndrome might benefit from an analysis of hypothalamic–pituitary axis function.

Declarations

Acknowledgments

The authors would like to thank the physicians, radiologists, laboratory staff, and nurses at Chulabhorn Hospital who contributed to the management of COVID-19 patients. We also thank Mullika Buttakosa for assistance conducting the study.

Authors' Contributions

TP and KT contributed to the conception or design of the study, data analysis, and interpretation. Data collection was performed by TP, BD, SS, and PT. TP was an important contributor to the writing of the manuscript. KT critically reviewed and revised the manuscript. All authors gave final approval for publication.

Data availability

The datasets used and/or analysed during current study available from the corresponding author on reasonable request.

Competing Interests

All authors have declared that there are no financial conflicts of interest with regard to this work.

Funding

This work was supported by the Chulabhorn Royal Academy (grant number RAA 2565/032). The funding body played no role in the study design; data collection, analysis, or interpretation; manuscript writing; or the decision to submit the article for publication

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Figures

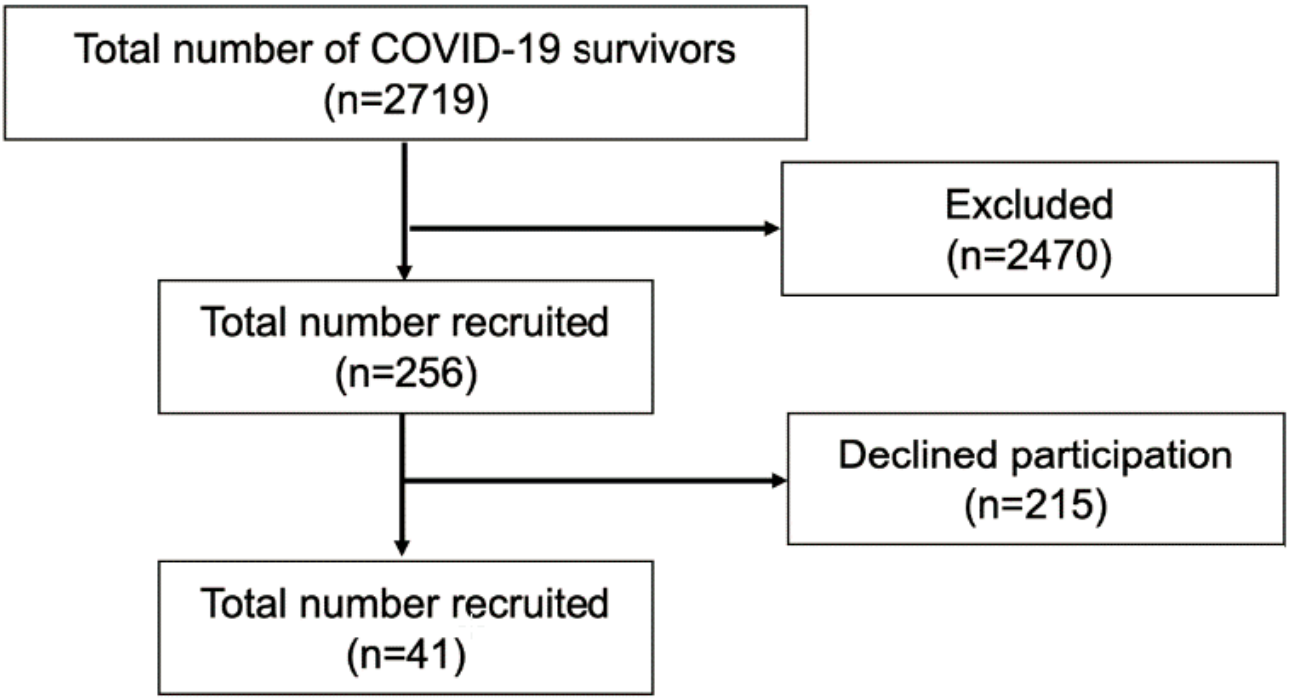

Figure 1

Study participation

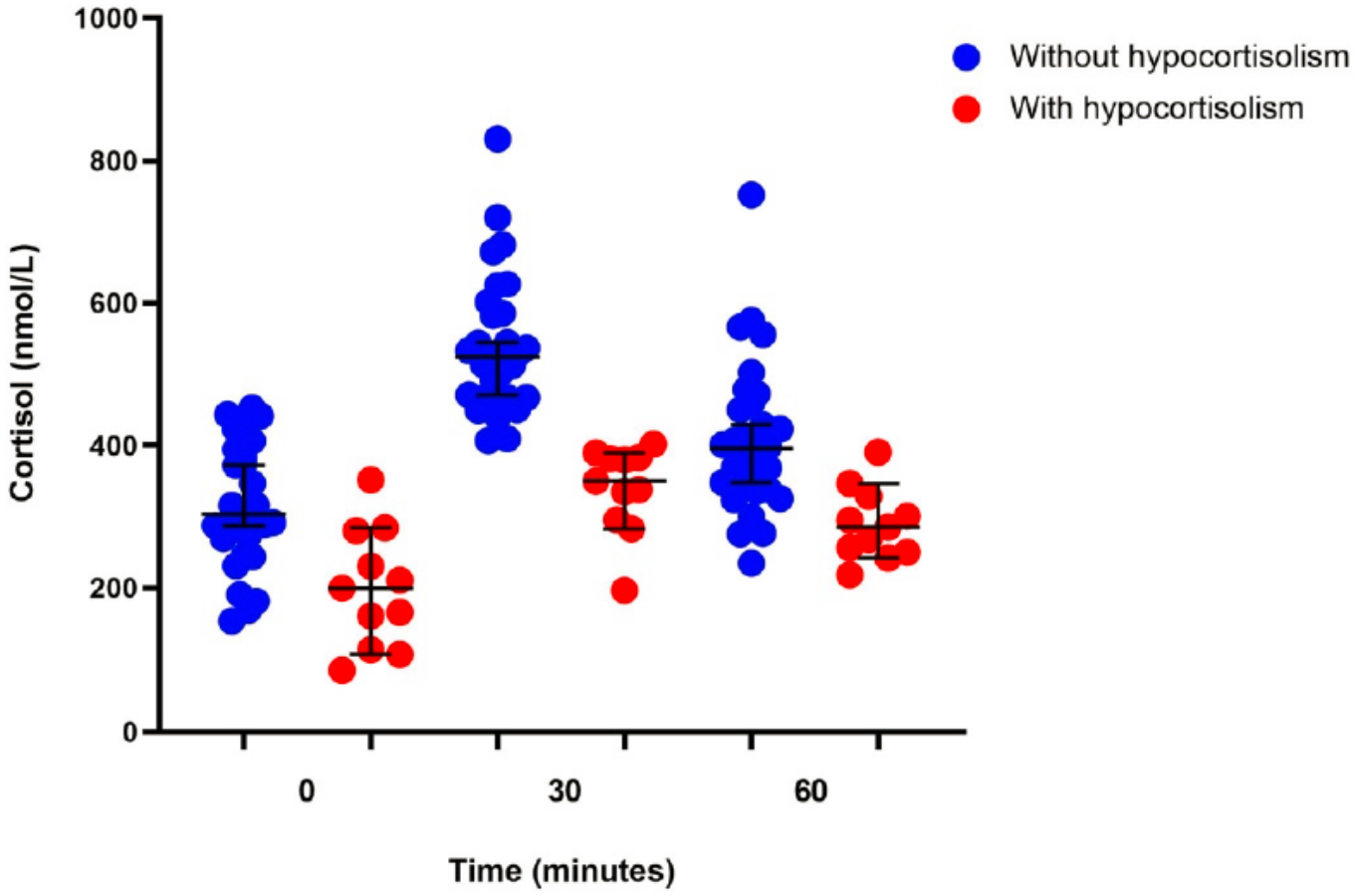

Figure 2

Corticotropin stimulation test results in patients with (n = 11) or without (n = 30) hypocortisolism

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